

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference JEC/BP5237227	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 96/ 02061	International filing date (day/month/year) 23/08/1996	(Earliest) Priority Date (day/month/year) 23/08/1995
Applicant CANCER RESEARCH CAMPAIGN TECHNOLOGY...et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☒ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. 1 ☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/02061

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/86 C12N5/10 C12N15/67

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF VIROLOGY 69 (7). 1995. 4086-4094. ISSN: 0022-538X, July 1995, XP002023654 LUUKKONEN B G M ET AL: "Efficiency of reinitiation of translation on human immunodeficiency virus type 1 mRNAs is determined by the length of the upstream open reading frame and by intercistronic distance." see the whole document ---	1-29
A	VIROLOGY (1995), 208(1), 215-25 CODEN: VIRLAX;ISSN: 0042-6822, 1 April 1995, XP002023655 HERZOG, ETIENNE ET AL: "Translation of the second gene of peanut clump virus RNA 2 occurs by leaky scanning in vitro" see the whole document --- -/--	1-29



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

23 January 1997

Date of mailing of the international search report

12.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Hornig, H

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. VIROL. (1993), 67(8), 4886-95 CODEN: JOVIAM;ISSN: 0022-538X, August 1993, XP000616337 FOUILLOT, NATHALIE ET AL: "Translation of the hepatitis B virus P gene by ribosomal scanning as an alternative to internal initiation" see the whole document ---	1-29
A	VIROLOGY, vol. 188, no. 1, May 1992, ACADEMIC PRESS, INC.,NEW YORK, US, pages 342-352, XP002023656 C.-G. LIN AND S.J. LO: "Evidence for involvement of a ribosomal leaky scanning mechanism in the translation of the hepatitis B virus Pol gene from the viral pregenome RNA" see the whole document ---	1-29
A	VIROLOGY, vol. 185, no. 2, December 1991, ACADEMIC PRESS, INC.,NEW YORK, US, pages 862-866, XP000616129 F.-L. COSSET ET AL.: "Newcastle disease virus (NDV) vaccine based on immunization with avian cells expressing the NDV hemagglutinin-neuraminidase glycoprotein" cited in the application see the whole document ---	1-29
A	MOL. CELL. BIOL., vol. 7, no. 10, October 1987, ASM WASHINGTON, DC,US, pages 3438-3445, XP000616288 M. KOZAK: "Effects of intercistronic length on the efficiency of reinitiation by eucaryotic ribosomes" cited in the application see the whole document ---	1-29
A	EXPRIMENTAL CELL RESEARCH, vol. 197, no. 2, December 1991, ACADEMIC PRESS INC., NEW YORK, US, pages 229-233, XP000616323 M. IZUMI ET AL.: "Blasticidin S-resistance gene (bsr): a novel selectable marker for mammalian cells" cited in the application see the whole document --- -/--	1-29

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NATURE (LONDON) (1984), 309(5963), 82-5 CODEN: NATUAS;ISSN: 0028-0836, 3 May 1984, XP002023657 LIU, CHUNG CHENG ET AL: "Initiation of translation at internal AUG codons in mammalian cells" see the whole document ---	1-29
A	WO,A,94 24870 (BIOTRANSPLANT INC ;GEN HOSPITAL CORP (US); LE GUERN CHRISTIAN A (U) 10 November 1994 see the whole document ---	1-29
A	WO,A,93 03143 (ANDERSON W FRENCH ;MORGAN RICHARD A (US); COUTURE LARRY (US)) 18 February 1993 see the whole document ---	1-29
A	WO,A,94 23048 (US HEALTH ;EIDEN MARYBETH V (US); WILSON CAROLYN A (US); DEACON NI) 13 October 1994 see the whole document ---	1-29
A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 85, no. 17, 1 September 1988, pages 6460-6464, XP000569693 DANOS O ET AL: "SAFE AND EFFICIENT GENERATION OF RECOMBINANT RETROVIRUSES WITH AMPHOTROPIC AND ECOTROPIC HOST RANGES" see the whole document ---	1-29
P,X	J. VIROL. (1995), 69(12), 7430-6 CODEN: JOVIAM;ISSN: 0022-538X, December 1995, XP000569527 COSSET, FRANCOIS-LOIC ET AL: "High-titer packaging cells producing recombinant retroviruses resistant to human serum" see the whole document -----	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/02061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9424870	10-11-94	AU-A- 6230394	21-11-94
		CA-A- 2162056	10-11-94
		EP-A- 0706319	17-04-96

WO-A-9303143	18-02-93	CA-A- 2114416	18-02-93
		EP-A- 0598029	25-05-94
		JP-T- 6509713	02-11-94

WO-A-9423048	13-10-94	AU-A- 6903194	24-10-94
		CA-A- 2160034	13-10-94
		EP-A- 0699240	06-03-96
		JP-T- 8511156	26-11-96

PCT

**NOTIFICATION OF THE RECORDING
OF A CHANGE**

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

CALDERBANK, T., R.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year) 01 September 1997 (01.09.97)
Applicant's or agent's file reference JEC/BP5237227
International application No. PCT/GB96/02061

IMPORTANT NOTIFICATION
International filing date (day/month/year) 23 August 1996 (23.08.96)

1. The following indications appeared on record concerning:

☒ the applicant
 ☒ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address COSSET, François-Lois 32, rue L.-Thévenet F-69004 Lyon FRANCE	State of Nationality FR	State of Residence FR
Telephone No.		
Facsimile No.		
Teleprinter No.		

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

Name and Address COSSET, François-Lois 30, grande rue de la Guillotière F-69007 Lyon FRANCE	State of Nationality FR	State of Residence FR
Telephone No.		
Facsimile No.		
Teleprinter No.		

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned
☐ the International Searching Authority
 ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority
 ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer F. Gateau Telephone No.: (41-22) 338.83.38
--	--

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing:

06 March 1997 (06.03.97)

International application No.:

PCT/GB96/02061

Applicant's or agent's file reference:

JEC/BP5237227

International filing date:

23 August 1996 (23.08.96)

Priority date:

23 August 1995 (23.08.95)

Applicant:

COLLINS, Mary, Katharine, Levinge et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

05 February 1997 (05.02.97)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 730.91.11

PCT

REC'D 24 JUN 1997

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JEC/BP5237227	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 96/ 02061	International filing date (day/month/year) 23/08/1996	Priority date (day/month/year) 23/08/1995
International Patent Classification (IPC) or national classification and IPC C12N15/86		
Applicant CANCER RESEARCH CAMPAIGN TECHNOLOGY LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This **REPORT** consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 05/02/1997	Date of completion of this report 20.06.97
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  A. Ury Telephone No. 5411

INTERNATIONAL PRELIMINARY EXAMINATION REPORT.

Intern. application No.

PCT/GB96/02061

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

☒ the international application as originally filed.

☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____,

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____.
☐ the claims, Nos. _____.
☐ the drawings, sheets/fig _____.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/GB96/02061

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-29 _____	YES
	Claims _____	NO
Inventive Step (IS)	Claims 1-29 _____	YES
	Claims _____	NO
Industrial Applicability (IA)	Claims 1-29 _____	YES
	Claims _____	NO

2. CITATIONS AND EXPLANATIONS

The following documents have been considered for the purposes of this report:

D1: Virol., 185(2), 1991, pp.862-66

D2: J. Virol., 69(12), Dec. 1995, pp.7430-36.

I) The subject-matter of the present set of claims is novel (Article 33.2 PCT) over the prior art documents cited in the International Search Report (ISR).

II) The problem underlying the present application can be defined as the provision of an expression system in which a gene of interest is expressed at an optimal level.

The solution proposed is based on the use of the inefficiency associated with the translation reinitiation process in a recombinant expression vector as defined in present claim 1.

The reinitiation of translation being a relatively inefficient process, the product of the selectable marker

gene is expressed at lower levels than the product of the gene of interest. This ensures that during the subsequent selection procedure, only those cell clones which express the gene of interest at higher or optimal levels will survive the other will be eliminated by the selection process.

Document D1 (which can be considered to represent the closest prior art document amongst those cited in the ISR) also discloses (see in particular page 862, right column and Fig.1) an expression vector comprising a gene of interest (Hn) and a selectable marker gene (Neo). The main difference between the present invention and D1 is the following. According to the present invention the selectable marker is arranged downstream of the gene of interest whereas in D1 the selectable marker is arranged upstream of the gene of interest. Thus, in D1 the marker gene is not expressed at a lower level than the product of the gene of interest and the effect obtained with the expression vector of the invention (namely, when the marker protein is expressed at detectable levels, the gene of interest is expressed at higher levels) is not achieved.

The use of the translation reinitiation process for the construction of the present recombinant expression vector was not derivable in an obvious manner from D1 alone or combined with other documents cited in the ISR. Therefore, the present set of claims fulfil the requirements of Article 33.3 PCT.

III) The priority documents pertaining to the present application were not available at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D2 cited in the ISR could become relevant.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 14 is not clear. Said claim refers to "the recombinant expression vector" whereas claim 10 defines two recombinant expression vectors (a first and a second).

The same remark accounts mutatis mutandis for claim 15 for the expressions "the retroviral vector" and "the packaging-deficient construct".